What’s New in Diabetes: 2017

Egils Bogdanovics M.D.
Hungerford Diabetes Center
Insulin: January 11, 1922

• 12 year old Leonard Thompson, on a starvation diet for 2 years received his first insulin injection

• A “thick brown muck” prepared by Banting and Best – 7.5cc in each buttock lowered glucose from 440 to 320 and resulted in an abscess at each injection site
Diabetes 2017

- Type 2: SGLT-2i and GLP1RA
- Type 2: Cardiovascular Outcome Trials
- Type 1 and 2: Insulin and Hypoglycemia
- Type 1 and 2: Continuous Glucose Monitoring
## 2017: 12 Classes of Drugs for Diabetes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Year of approval</th>
<th>HbA1c reduction with monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Parenteral</td>
<td>1921</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.5</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>1995</td>
<td>1.5</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Oral</td>
<td>1995</td>
<td>0.5-0.8</td>
</tr>
<tr>
<td>Thiazoladenediones</td>
<td>Oral</td>
<td>1997</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Metiglinides</td>
<td>Oral</td>
<td>1997</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>GLP-1 analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Amylin Analogs</td>
<td>Parenteral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Oral</td>
<td>2006</td>
<td>0.5-0.9</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Oral</td>
<td>2008</td>
<td>0.5</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Oral</td>
<td>2009</td>
<td>0.7</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Oral</td>
<td>2013</td>
<td>0.9</td>
</tr>
</tbody>
</table>
The Ominous Octet

- Islet \( \beta \)-cell: Impaired Insulin Secretion
- Islet \( \alpha \)-cell: Increased Glucagon Secretion
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Increased HGP
- Neurotransmitter Dysfunction

DeFronzo RA *Diabetes* 2009
Phlorizin 1835
The Kidney and Glucose Homeostasis

~180 g of glucose filtered per day

S1 segment of proximal tubule

~90%

SGLT-2

Reabsorption

~180 g/d

Distal S2/S3 segment of proximal tubule

~10%

SGLT-1

Collecting duct

Virtually no glucose excreted in the urine

The Newest Antihyperglycemic Class

SGLT2 Inhibitors

SGLT2 inhibitors suppress the action of SGLT2

Increase urinary glucose excretion

Lost in urine

Reduce glucose reabsorption

Glucose

SGLT2

SGLT2 inhibitor

Renal Threshold for Glucose Excretion in Healthy Subjects

There is a Threshold Relationship Between Plasma Glucose and UGE

- **Urine Glucose Excretion (g/day)**
  - 0
  - 25
  - 50
  - 75
  - 100
  - 125

- **Plasma Glucose (mg/dL)**
  - 0
  - 50
  - 100
  - 150
  - 200
  - 250
  - 300

**Healthy Subjects**
- $R_T^G \sim 180 \text{ mg/dL}$

*Renal threshold for glucose

*(FDA Advisory Committee Sponsor Slide Presentation 10Jan2013)*
Renal Threshold for Glucose Excretion in T2DM: Increased
SGLT2 Inhibition Lowers Renal Threshold for Glucose Excretion
SGLT2 Inhibitors

- INVOKANA canagliflozin
- FARXIGA dapagliflozin
- JARDIANCE empagliflozin
  sotagliflozin
Guidelines
**Approach to the Management of Hyperglycemia**

<table>
<thead>
<tr>
<th>Patient/Disease Features</th>
<th>More Stringent</th>
<th>A1C 7%</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks associated with hypoglycemia &amp; other drug adverse effects</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude &amp; expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
<td></td>
</tr>
<tr>
<td>Resources &amp; support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

*American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2016; 39 (Suppl. 1): S39-S46*

Evolution of FDA CV Safety Concerns

• 1992 Human Proinsulin: trials and development suspended due to increased risk acute MI
• 2005 Muraglitazar: increased risk of death, major CV events, CHF
• 2007 Rosiglitazone: increased CV risk; withdrawn from market in many countries*
• 2008: FDA Guidance
Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Additional copies are available from:
Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

December 2008
3 point “MACE”: Major Adverse Cardiovascular Event

- Cardiovascular Death
- Non-Fatal Myocardial Infarction
- Non-Fatal Stroke
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med
Volume 373(22):2117-2128
November 26, 2015
Glycated Hemoglobin Levels.

Cardiovascular Outcomes and Death from Any Cause.

Death From CV Cause

HR 0.62 (95% CI: 0.49, 0.77)
P < .0001

## EMPA-REG CV death, MI and stroke

<table>
<thead>
<tr>
<th>Patients with event/analysed</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>490/4687</td>
<td>282/2333</td>
<td>0.86</td>
<td>(0.74, 0.99)*</td>
<td>0.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>172/4687</td>
<td>137/2333</td>
<td>0.62</td>
<td>(0.49, 0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>213/4687</td>
<td>121/2333</td>
<td>0.87</td>
<td>(0.70, 1.09)</td>
<td>0.2189</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>150/4687</td>
<td>60/2333</td>
<td>1.24</td>
<td>(0.92, 1.67)</td>
<td>0.1638</td>
</tr>
</tbody>
</table>

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction

*95.02% CI
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin\(^1\) for 5.4 years

- High CV risk
- 5% diabetes, 26% hypertension

NNT: 30

Ramipril\(^2\) for 5 years

- High CV risk
- 38% diabetes, 46% hypertension

NNT: 56

Empagliflozin

- T2DM with high CV risk
- 92% hypertension

NNT: 39

Pre-ACEi/ARB era

- >80% ACEi/ARB

Pre-statin era

- <29% statin

1. 4S investigator. Lancet 1994; 344: 1383-89, [http://www.trialresultscenter.org/study2590-4S.htm](http://www.trialresultscenter.org/study2590-4S.htm);
Original Article

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group

N Engl J Med
Volume 377(7):644-657
August 17, 2017
Effects of Canagliflozin on Glycated Hemoglobin Level, Body Weight, and Systolic and Diastolic Blood Pressure in the Integrated CANVAS Program.

Cardiovascular Outcomes in the Integrated CANVAS Program.

A  Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

No. at Risk  Placebo  Canagliflozin
4347  4239  4153  4061  2942  1626  1240  1217  1187  1156  1120  1095  789  216
5795  5672  5566  5447  4343  2984  2555  2513  2460  2419  2363  2311  1661  448

Hazard ratio, 0.86 (95% CI, 0.75–0.97)
P<0.001 for noninferiority
P=0.02 for superiority

B  Death from Cardiovascular Causes

No. at Risk  Placebo  Canagliflozin
4347  4116  4279  4236  3119  1759  1356  1344  1328  1310  1292  1280  924  258
5795  5768  5723  5679  4576  3182  2761  2736  2710  2687  2651  2615  1904  532

Hazard ratio, 0.87 (95% CI, 0.72–1.06)

C  Nonfatal Stroke

No. at Risk  Placebo  Canagliflozin
4347  4270  4197  4123  3004  1667  1274  1255  1232  1208  1177  1155  829  232
5795  5702  5615  5530  4414  3043  2621  2588  2543  2511  2464  2415  1751  481

Hazard ratio, 0.90 (95% CI, 0.71–1.15)

D  Nonfatal Myocardial Infarction

No. at Risk  Placebo  Canagliflozin
4347  4256  4187  4109  2986  1647  1255  1233  1207  1179  1146  1126  812  223
5795  5711  5625  5533  4405  3029  2602  2565  2516  2476  2425  2382  1728  468

Hazard ratio, 0.85 (95% CI, 0.69–1.05)

Cardiovascular Outcomes in the Integrated CANVAS Program

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>
### Table 2. Adverse Events. *

<table>
<thead>
<tr>
<th>Event</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>104.3</td>
<td>120.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>35.5</td>
<td>32.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Serious and nonserious adverse events of interest recorded in the CANVAS Program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis (adjudicated)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.63</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell</td>
<td>0.6</td>
<td>0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.0</td>
<td>1.1</td>
<td>0.74</td>
</tr>
<tr>
<td>Breast</td>
<td>3.1</td>
<td>2.6</td>
<td>0.65</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1.0</td>
<td>0.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetic ketoacidosis (adjudicated)</td>
<td>0.6</td>
<td>0.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Amputation</td>
<td>6.3</td>
<td>3.4</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Fracture (adjudicated):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>15.4</td>
<td>11.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Low-trauma</td>
<td>11.6</td>
<td>9.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>1.7</td>
<td>1.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Infection of male genitalia‡</td>
<td>34.9</td>
<td>10.8</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Serious and nonserious adverse events of interest collected in CANVAS alone‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmotic diuresis</td>
<td>34.5</td>
<td>13.3</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>26.0</td>
<td>18.5</td>
<td>0.009†</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>50.0</td>
<td>46.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3.0</td>
<td>4.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>6.9</td>
<td>4.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>40.0</td>
<td>37.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Mycotic genital infection in women</td>
<td>68.8</td>
<td>17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe hypersensitivity or cutaneous reaction</td>
<td>8.5</td>
<td>6.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Hepatic injury</td>
<td>7.4</td>
<td>9.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Renal-related (including acute kidney injury)</td>
<td>19.7</td>
<td>17.4</td>
<td>0.32</td>
</tr>
</tbody>
</table>

* Analyses were performed on data from the on-treatment data set (patients who had a safety outcome while they were receiving canagliflozin or placebo or within 30 days after discontinuation of the drug or placebo), except for fracture, amputation, cancer, and diabetic ketoacidosis outcomes, which included all events at any time point in all patients who underwent randomization and received at least one dose of canagliflozin or placebo.  
† P values were estimated from Cox regression models.  
‡ Low-trauma fracture was the prespecified primary fracture outcome, and all fracture was a secondary outcome.  
§ Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.  
¶ For these adverse events, the annualized incidence rates are reported with data from CANVAS alone through January 7, 2014, because after this time, only serious adverse events or adverse events leading to discontinuation were collected. In CANVAS-R, only serious adverse events or adverse events leading to discontinuation were collected. Owing to the differences between the two trials in methods of collection of the data, an integrated analysis of these adverse events is not possible.
Conclusions

- In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.
Large CV Outcomes Trials in T2D

La Barre proposed the name “Incretin” for an intestinal derived factor which lowered glucose.

LEADER trial: Primary Outcome

First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk.

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP et al., NEJM 2016
LEADER trial: Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial

Adapted from: Marso SP et al., NEJM 2016
Large CV Outcomes Trials in T2D

SAVOR N
EXAMINE N


TECOS N
LEADER B
ELIXA N
EMPA REG B

SUSTAIN 6 B
EXSCEL
NCT01986881

CARMELINA
CAROLINA
CANVAS

REWIND
DECLARE

DPP-4 inhibitor
SGLT2 inhibitor
GLP-1 RA

Semaglutide Cardiovascular Outcomes.

- **A Primary Outcome**
  - Hazard ratio, 0.74 (95% CI, 0.58–0.95)
  - P<0.001 for noninferiority
  - P=0.02 for superiority

- **B Nonfatal Myocardial Infarction**
  - Hazard ratio, 0.74 (95% CI, 0.51–1.08)
  - P=0.12

- **C Nonfatal Stroke**
  - Hazard ratio, 0.61 (95% CI, 0.38–0.99)
  - P=0.04

- **D Death from Cardiovascular Causes**
  - Hazard ratio, 0.98 (95% CI, 0.65–1.48)
  - P=0.92

No. at Risk
- **A**
  - Placebo: 1649, 1616, 1586, 1567, 1534, 1508, 1479
  - Semaglutide: 1648, 1619, 1601, 1584, 1568, 1543, 1524

- **B**
  - Placebo: 1649, 1624, 1598, 1587, 1562, 1542, 1516
  - Semaglutide: 1648, 1623, 1609, 1595, 1582, 1560, 1543

- **C**
  - Placebo: 1649, 1629, 1611, 1597, 1571, 1548, 1528
  - Semaglutide: 1648, 1630, 1619, 1606, 1593, 1572, 1558

- **D**
  - Placebo: 1649, 1637, 1623, 1617, 1600, 1584, 1566
  - Semaglutide: 1648, 1634, 1627, 1617, 1607, 1589, 1579
Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes


N Engl J Med
Volume 377(13):1228-1239
September 28, 2017
EXCEL Trial Outcomes

A Primary Cardiovascular Outcome

Hazard ratio, 0.91 (95% CI, 0.83–1.00)
P = 0.001 for noninferiority
P = 0.06 for superiority

B Death from Any Cause

Hazard ratio, 0.86 (95% CI, 0.77–0.97)

C Death from Cardiovascular Causes

Hazard ratio, 0.88 (95% CI, 0.76–1.02)

D Hospitalization for Heart Failure

Hazard ratio, 0.94 (95% CI, 0.78–1.13)

CV risk in T2D: summary of large randomized trials with respect to CV events (MACE), CV mortality, and heart failure.

<table>
<thead>
<tr>
<th></th>
<th>CV Events</th>
<th>CV Mortality</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive vs. less intensive glycemic control</td>
<td></td>
<td></td>
<td>Admission to hospital/fatal heart failure</td>
</tr>
<tr>
<td>ACCORD</td>
<td>←</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>Individual glucose-lowering drug vs. placebo (since 2008 FDA guidance)</td>
<td></td>
<td></td>
<td>Hospitalization for heart failure</td>
</tr>
<tr>
<td>ELIXA</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>EXAMINE</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>SAVOR-TIMI 53</td>
<td>←</td>
<td>←</td>
<td>↑ (HR 1.27)</td>
</tr>
<tr>
<td>TECOS</td>
<td>←</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>↓ (HR 0.86)</td>
<td>↓ (HR 0.62)</td>
<td>↓ (HR 0.65)</td>
</tr>
<tr>
<td>LEADER</td>
<td>↓ (HR 0.87)</td>
<td>↓ (HR 0.78)</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>↓ (HR 0.74)</td>
<td>←</td>
<td></td>
</tr>
<tr>
<td>CANVAS</td>
<td>↓ (HR 0.86)</td>
<td>←</td>
<td>↓ (HR 0.67)</td>
</tr>
</tbody>
</table>

Bernard Zinman et al. Dia Care 2017;40:1302-1313
Insulin
Pancreatic Poop-Out in Type 2 Diabetes

*IGT=impaired glucose tolerance.
International Diabetes Center, 2000
Decline in $\beta$ Cell Function in UKPDS

Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS. Lebovitz H. *Diabetes Rev.* 1999;7:139-153.

Rx: Insulin, metformin, sulfonylurea
Insulin 1928
Insulin concentrations

- 1922 U-5
- 1923 U-10 and U-20
- 1924 U-40
- 1925 U-80
- 1972 U-100 adopted
- 1958 U-500 Reg Beef
- 1998 U-500 Reg Hum
- 2015 U-200 Lispro
- 2015 U-300 Glargine
- 2015 U-200 Degludec
PK Profile of Currently Available Insulins

- Inhaled insulin
- Aspart, Lispro, Glulisine
- Regular
- Intermediate (NPH insulin)
- Long (Insulin glargine; Insulin detemir; Insulin glargine equivalent)
- Ultralong (U300 glargine; Insulin degludec)

New Basal Insulins
Basal/Bolus Treatment Program with Rapid-acting and Long-acting Analogs

Plasma insulin

Breakfast: Novolog, Humalog, or Apidra
Lunch: Aspart, Lispro, or Glulisine
Dinner: Aspart, Lispro, or Glulisine
Basal Insulin

• NPH
• Glargine: Lantus and Toujeo
• Detemir: Levemir
• Degludec: Tresiba
Contribution to overall hyperglycemia (%)

A1C value quintiles (%)

N=290 non–insulin-using patients with type 2 diabetes.


- Findings revealed that as A1C improves, the relative contribution of PPG becomes increasingly important in maintaining overall glycemic control.
Progressive Deterioration of PPG and FPG Is Characteristic of Type 2 Diabetes

Insulin Glargine U-300
Glargine U-300

Graph showing GIR* over time after subcutaneous injection (hours) for different treatments:
- **Toujeo 0.4 units/kg** (green line)
- **Insulin glargine (100 units/ml) 0.4 units/kg** (blue dotted line)
Glargine U-300

- FDA approved February 25, 2015
- Three times as concentrated as glargine U-100
- Longer duration of action (36 hours or less) than glargine U-100; half-life about 23 hours
- Less variable plasma insulin exposure
- Similar safety and efficacy profile as U-100
## Glargine U-300 vs Glargine U-100 in Type 2 Diabetes Meta-Analysis

### Baseline to Month 6

<table>
<thead>
<tr>
<th></th>
<th>Glargine U-300 (n=1247)</th>
<th>Glargine U-100 (n=1249)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%), LS mean</td>
<td>-1.02</td>
<td>-1.02</td>
<td>Not specified</td>
</tr>
<tr>
<td>Weight (kg), LS mean</td>
<td>0.49</td>
<td>0.75</td>
<td>P = .058</td>
</tr>
<tr>
<td>Any hypoglycemia in 24 hr*</td>
<td>67.8</td>
<td>73.8</td>
<td>0.92 (0.87-0.96)</td>
</tr>
<tr>
<td>Any nocturnal hypoglycemia*</td>
<td>31.7</td>
<td>41.3</td>
<td>0.77 (0.69-0.85)</td>
</tr>
</tbody>
</table>

*Percent people with 1 or more events.


- Titrate dose every 3 days
- Higher daily dose may be needed
Insulin Degludec
Insulin Degludec

**desB30 insulin**
- Acylated (16 carbon fatty acid chain) at LysB29

**PK**
- Onset: 2 to 4 h
- Half life: \(~\)25 h
- Duration of action: \(\geq\) 42 h
- Steady state: \(~\)3 to 4 d
- Detectable: \(\geq\) 5 d
- 36-h stable level

**FDA approval in 2015**

Insulin Degludec

- FDA approved September 25, 2015
- Prolonged action profile
- Formation of multihexamers
- Half-life of about 25 hours
- Duration of action longer than 42 hours
- Flat PK/PD profile of both 100 U/mL and 200 U/mL formulations
Degludec Titration

Relative serum trough concentrations of once-daily dosing in adults with type 1 diabetes\textsuperscript{2,3}

STEADY STATE ACHIEVED AFTER 3 TO 4 DAYS\textsuperscript{1}
Degludec Variable Dosing\(^\d\) vs Glargine U100 or Degludec Dosed Regularly\(^*\)

Variable dosing with degludec had similar efficacy and similar hypoglycemia compared with either regular dosing regimen.

\(^*\)687 patients with T2D in a 26-wk, randomized, open-label, parallel-group, treat-to-target trial; 
\(^\d\)Dosing schedule provided for a maximum dosing interval of 40 h and a minimum dosing interval of 8 h; 
\(^\d\)Morning defined as time period from waking up to first meal of day; 
\(^\dd\)Evening defined as time period from start of evening meal to bedtime.

Glycaemic control: variability

Hyperglycaemia

Hypoglycaemia

Mean BG ≈ HbA₁c 7.8%
(61.7 mmol/mol)

BG, blood glucose

Pathophysiological cardiovascular consequences of hypoglycaemia


Effects last up to 7 days

Persists for up to 48 hours

Blood coagulation abnormalities

Neutrophil activation

Platelet activation

Factor VIII

CRP

VEGF

IL-6

Inflammation

Epinephrine

Haemodynamic changes

Heart rate variability

Rhythm abnormalities

Heart workload

Contractility

Output

Sympathoadrenal response

Endothelial dysfunction

Vasodilatation

Heart rate variability

Rhythm abnormalities

Haemodynamic changes

↑ Heart workload

↑ Contractility

↑ Output

↑ Epinephrine

↑ Platelet activation

↑ Neutrophil activation

Blood coagulation abnormalities
Hypoglycaemia is associated with ECG abnormalities

- Abnormalities in:
  - Atrioventricular conduction
  - Ventricular repolarisation
- Catecholamine release leads to:
  - ↓K+
  - R-wave amplification
  - T-wave flattening
  - Depression of ST segment
  - Prolongation of QT interval
- Risk of cardiac arrhythmia

ECG, electrocardiogram
DEVOTE confirmed the cardiovascular safety of insulin degludec in comparison with insulin glargine (both U100).

DEVO confirmed 752 adjudication-confirmed severe hypoglycaemic events in a blinded head-to-head trial.

A 40% lower rate of severe hypoglycaemia was confirmed at similar levels of HbA$_1$c.

A 53% lower rate of nocturnal severe hypoglycaemia was confirmed at a lower fasting plasma glucose.

CI, confidence interval; EAC, Event Adjudication Committee; HR, hazard ratio; IGlar U100, insulin glargine U100; MACE, major adverse cardiovascular events; N, number of patients at risk; PYO, patient-years of observation.

New Basal Insulins

• Reduced Intrasubject Variability
• True 24 Hour Duration
• Reduced Nocturnal Hypoglycemia
• Reduced Injection Burden in T2DM
Detecting Glucose Variability with SMBG

- SMBG testing is associated with improved A1C levels in patients with T1DM and patients with T2DM treated with insulin.

- Efficacy of SMBG depends on the patient’s willingness and ability to perform several finger sticks throughout the day.

- Even when SMBG frequency is high, it still provides only a few snapshots from a complex and variable environment, and provides no information about glucose levels when a patient is sleeping.
Blood Glucose Fluctuations in Patients with Similar Average Blood Glucose Values


Patient A

Mean BG=144; A1C=6.5%
Hypoglycemia: ≤70 mg/dL

Patient B

Mean BG=144; A1C=6.5%
Hypoglycemia: ≤70 mg/dL
Continuous Glucose Monitoring (CGM)
Continuous Glucose Monitor Sensor
Where is the ball going?
HbA1c 7.3 Sensor Modal Day Report
Hypoglycemia Unawareness

“with Freddie, no reaction occurred after a blood sugar of 60 mg/dl and with Alice S., none occurred when the blood sugar was as low as 40 ... Dangerous hypoglycemia may occur without warning symptoms.”

Joslin, E  1924
Trend Arrow
• 81% of CGM users openly admitted to using CGM glucose values for determining insulin doses
Decision Making with CGM

- CGM number
- Trend Arrow
- Alert/Alarm
- Trend Graph
Trend Arrows
Know Your Dexcom CGM Arrows!

- Glucose rising
  - 3 mg/dL/min
  - 90+ mg/dL in 30 min
- Glucose rising
  - 2-3 mg/dL/min
  - 60-90 mg/dL in 30 min
- Glucose rising
  - 1-2 mg/dL/min
  - 30-60 mg/dL in 30 min
- Glucose changing
  - <1 mg/dL/min
  - 0-30 mg/dL in 30 min
- Glucose falling
  - 1-2 mg/dL/min
  - 30-60 mg/dL in 30 min
- Glucose falling
  - 2-3 mg/dL/min
  - 60-90 mg/dL in 30 min
- Glucose falling
  - >3 mg/dL/min
  - 90+ mg/dL in 30 min

www.CGMonitoring.net
Goal: Try to stay between the lines

As your skills improve, lower the glucose for the upper alert
Hypoglycemia
Hypoglycemia

Are you low or just stupid?
Using a CGM: Change in Time Spent Within Various Glucose Ranges

Subjects with Baseline A1C > 9%

<table>
<thead>
<tr>
<th>Glucose Range (mg/dL)</th>
<th>Median % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>-31.1%</td>
</tr>
<tr>
<td>55-80</td>
<td>27.4%</td>
</tr>
<tr>
<td>81-140</td>
<td>94.6%*</td>
</tr>
<tr>
<td>141-240</td>
<td>0.8%</td>
</tr>
<tr>
<td>&gt;240</td>
<td>-36.4%</td>
</tr>
</tbody>
</table>

Subjects with Baseline A1C ≤ 7%

<table>
<thead>
<tr>
<th>Glucose Range (mg/dL)</th>
<th>Median % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>-46.4%*</td>
</tr>
<tr>
<td>55-80</td>
<td>-14.5%</td>
</tr>
<tr>
<td>81-140</td>
<td>8.8%</td>
</tr>
<tr>
<td>141-240</td>
<td>-8.5%</td>
</tr>
<tr>
<td>&gt;240</td>
<td>-14.2%</td>
</tr>
</tbody>
</table>

*p < 0.05
Could real-time CGM also be successful in patients with MDI?

Comparison of different treatment modalities for Type 1 diabetes including Sensor-Augmented Insulin Regimens in 52-weeks follow-up: a COMISAIR study (Soupal J. et al. 2016)¹

¹. Soupal J et al. 2016 (under consideration for publication)
Could real-time CGM also be successful in patients with MDI?

Comparison of different treatment modalities for Type 1 diabetes including Sensor-Augmented Insulin Regimens in 52-weeks follow-up: a COMISAIR study (Soupal J. et al. 2016)¹

![Graph comparing different insulin regimens](image)

Sensor-augmented insulin regimens

Reduction of glycemic variability ($SD_T$)*

1. Soupal J et al. 2016 (under consideration for publication)
“Therapeutic” CGM

• 12/20/16 FDA expanded indication Dexcom G5 CGM to replace FSBG testing for treatment decisions: “non-adjunctive” use

• 1/12/17 CMS ruling 1682R classified Therapeutic vs Non-Therapeutic CGM systems for Medicare patients
Medicare Therapeutic CGM

• Have Type 1 or Type 2 Diabetes
• Currently use a Home Blood Glucose Monitor and perform at least 4 fingersticks per day
• Take insulin, either with multiple daily injections or an insulin pump pump
• Have an insulin plan that requires frequent changes based on CGM readings
Freestyle Libre
Artificial Pancreas
Artificial Pancreas 670G
“The person with diabetes who knows the most lives the longest”

Elliot Joslin